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## PATENT SPECIFICATION

624,117



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## PROVISIONAL SPECIFICATION

### Improvements in and relating to the Preparation of Substituted Allylamines and Propylamines

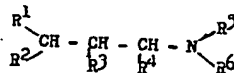
We, THE WELLCOME FOUNDATION LIMITED, of 183—193, Euston Road, London, N.W.1, (a British Company), and DONALD WALLACE ADAMSON, a British subject, of the Company's address, do hereby declare the nature of this invention to be as follows:—

This invention relates to a process for the preparation of new substituted allylamines and their conversion to substituted propylamines which have valuable therapeutic properties.

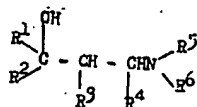
The object of our invention is to make possible the manufacture of certain novel substituted allylamines which are useful as starting materials for other production compounds.

A further object of our invention is to provide an improved process for the production of certain substituted propylamines which have valuable therapeutic properties, such process being more simple and convenient than the processes for producing such substituted propylamines hitherto known.

According to the process of our invention we make N-disubstituted- $\gamma$ -disubstituted allylamines of the formula



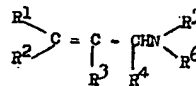
by the removal of the elements of water from the corresponding N-disubstituted- $\gamma$ -disubstituted- $\gamma$ -hydroxy propylamines of the formula



In each of the general formulæ just given  $R^1$  and  $R^2$  are either identical or different and may be aryl, aralkyl or hydro-

aromatic groups, which may be substituted by alkyl, alkoxy or other groups which are not affected by mild reduction conditions;  $R^3$  is hydrogen or alkyl;  $R^4$  is hydrogen, alkyl or aryl (optionally substituted as above);  $R^5$  and  $R^6$  are identical or different and are alkyl or aryl, or  $-NR^5R^6$  may denote the piperidino- or morpholino-groups.

According to a further feature of our invention, we convert the new substituted allylamines, described above, into N-disubstituted- $\gamma$ -disubstituted propylamines of the formula



(wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$  and  $R^6$  have the same meaning as above) by reduction under mild conditions.

The dehydration of other tertiary alcohols is a well-known process and may be carried out by a variety of agents. In the present case it has been found satisfactory to dissolve the substituted amino tertiary alcohol or a salt thereof (for example the hydrochloride) in a mixture of acetic acid and concentrated aqueous hydrochloric acid and reflux the solution for a period of 15 minutes to 1 hour. The solution is then evaporated to dryness under reduced pressure, the residue dissolved in water, excess of an alkali such as concentrated ammonia added, and the liberated base separated by extraction with an organic solvent such as ether. The base may be recovered by evaporation of the solvent and purified by distillation under reduced pressure, or alternatively, if the base is a solid, by recrystallisation from a solvent (e.g. petroleum ether).

Alternatively in some examples the base may be converted into a salt, particularly the hydrochloride, by treating the dried solution of the base in a solvent (for

example ether) with dry hydrogen chloride, when the hydrochloride separates and may be recrystallised, if necessary, from a solvent.

- 5 The manufacture of the N-disubstituted  $\gamma\gamma$ -disubstituted- $\gamma$ -hydroxy propylamines used as starting materials is described in the specification of our co-pending application for Letters Patent No. 36258/46  
 10 (Serial No. 624,118) of even date herewith. Examples of such starting materials are  $\gamma\gamma$ -diphenyl- $\gamma$ -hydroxy- $\alpha$ -piperidinopropane and  $\gamma\gamma$ -diphenyl- $\gamma$ -hydroxy- $\alpha$ -dimethylaminopropane.  
 15 The conditions employed in the reduction may be varied. The reduction may be carried out either on the free base in solution in ethyl alcohol or other solvent or on the hydrochloride of the base dissolved in water or in ethyl alcohol or other  
 20 solvent, using hydrogen at atmospheric pressure or at higher pressure, in the presence of a hydrogenation catalyst, as for example platinum black or palladised charcoal.  
 25 The manufacture by a different process of some of the N - substituted -  $\gamma\gamma$  - disubstituted propylamines which may be made by the process of our invention has already been described, for example  $\gamma\gamma$ -diphenyl -  $\alpha$  - diethylamino - propane  
 30 (Eisleb, *Berichte*, 1941, volume 74B, page 1433) and  $\gamma\gamma$ -diphenyl- $\alpha$ -piperidinopropane (Schaumann, *Medizin und Chemie*, 1942, volume 4, page 229). The  
 35 compounds have been claimed to be highly active spasmolytic agents and to be useful in the treatment of asthma.  
 40 The invention is illustrated by the following example, in which quantities are given in parts by weight.

- A solution of 15 parts  $\gamma\gamma$  - diphenyl- $\gamma$ -hydroxy -  $\alpha$  - piperidinopropane hydrochloride in 30 parts concentrated aqueous  
 45 hydrochloric acid and 100 parts glacial

acetic acid was refluxed for 30 minutes. The solution has then evaporated to dryness under reduced pressure and the residual solid dissolved in water and the free base liberated by addition of excess 50 ammonia solution and separated by extraction with ether. The ether solution was dried, the ether evaporated and the residual oil distilled under reduced pressure, when the product,  $\gamma\gamma$  - diphenyl- $\alpha$ - 55 piperidino- $\beta\gamma$ -propylene, was collected as a colourless liquid, boiling point 138°C. at 0.1 mm. pressure.

Dry hydrogen chloride was passed through a solution of 10 parts of the base 60 in 20 parts chloroform until acid to congo red and dry ether was added until crystallisation commenced. After standing for several hours the precipitate of  $\gamma\gamma$ -diphenyl -  $\alpha$  - piperidino -  $\gamma$  - propylene 65 hydrochloride was filtered off and recrystallised from a mixture of chloroform and acetone. It had melting point 209—210°C.

A solution of 5 parts of the hydro- 70 chloride in 50 parts ethyl alcohol was shaken at room temperature (17°C.) with 0.1 parts of platinum oxide (prepared according to the directions given in Organic Syntheses, 1932, Collective, 75 Volume 1, page 452) in an atmosphere of hydrogen. When the theoretical amount of hydrogen had been absorbed (after approximately 3 hours) the catalyst was removed by filtration and the alcohol 80 evaporated under reduced pressure. The solid residue was recrystallised from a mixture of alcohol and acetone when  $\gamma\gamma$  - diphenyl -  $\alpha$  - piperidinopropane hydrochloride was obtained as crystals, 85 melting point 215—217°C.

Dated this 7th day of December, 1946.

G. H. FRAZER,  
Chartered Patent Agent.

## COMPLETE SPECIFICATION

### Improvements in and relating to the Preparation of Substituted Allylamines and Propylamines

- We, THE WELLCOME FOUNDATION LIMITED, of 183—193, Euston Road, London, N.W.1, (a British Company),  
 90 and DONALD WALLACE ADAMSON, a British subject, of the Company's address, do hereby declare the nature of this invention and in what manner the same is to be performed, to be particularly described and ascertained in and by the following statement:—

This invention relates to a process for the preparation of new substituted allylamines and their conversion to substituted

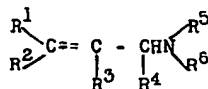
propylamines which have valuable therapeutic properties.

The object of our invention is to make possible the manufacture of certain novel substituted allylamines which have valuable therapeutic activity and are also useful as starting materials for the production of other therapeutically valuable compounds.

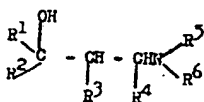
A further object of our invention is to provide an improved process for the production of certain substituted propylamines which have valuable therapeutic

properties, such process being more simple and convenient than the processes for producing such substituted propylamines hitherto known.

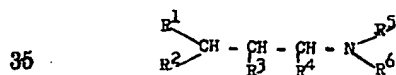
- 5 According to the process of our invention we make N - disubstituted -  $\gamma\gamma$  - disubstituted allylamines of the formula



- 10 or salts thereof by the removal of the elements of water (by known methods for the conversion of tertiary alcohols into olefinic compounds by dehydration) from the corresponding N-disubstituted- $\gamma\gamma$ -disubstituted -  $\gamma$  - hydroxypropylamines of the formula



- 20 or salts thereof. In each of the general formulae just given  $R^1$  and  $R^2$  are aryl, aralkyl or cycloalkyl groups, which may be substituted by alkyl, alkoxy or other groups which are not affected by mild reduction conditions;  $R^1$  and  $R^2$  may be identical, provided that both are not aralkyl groups;  $R^3$  is hydrogen or alkyl;  $R^4$  is hydrogen, alkyl or aryl (optionally substituted as above);  $R^5$  and  $R^6$  are identical or different and are alkyl or aryl, or  $-NR^5R^6$  may denote the piperidino-, pyrrolidino- or morpholino- groups.
- 30 According to a further feature of our invention, we convert the new substituted allylamines, described above, or their salts, into N - disubstituted -  $\gamma\gamma$  - disubstituted propylamines of the formula



(wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$  and  $R^6$  have the same meaning as above) by reduction under mild conditions.

- 40 As a matter of scientific accuracy it may be mentioned that when  $R^1$  or  $R^2$  is an aralkyl or cycloalkyl group or when both  $R^1$  and  $R^2$  are cycloalkyl groups, the allylamine formed by the dehydration step is sometimes an isomer of the allylamine whose general formula is given above, the isomer differing from that of the said general formula only in the position of the double bond and the hydrogen atom. Or the product may be a mixture
- 50 of such isomers. Both these isomers and

mixtures thereof are to be regarded as lying within the scope of our invention, the general formula for these allylamines being read with the position of the double bond and hydrogen atom optional. Both the isomers, of course, yield identical N-disubstituted -  $\gamma\gamma$  - disubstituted propylamines on reduction.

The dehydration of other tertiary alcohols is a well-known process and may be carried out by a variety of agents. In the present case it has been found satisfactory to dissolve the substituted amino tertiary alcohol or a salt thereof (for example the hydrochloride) in a mixture of acetic acid and concentrated aqueous hydrochloric acid and reflux the solution for a period of 15 minutes to 1 hour. The solution is then evaporated to dryness under reduced pressure, the residue dissolved in water, excess of an alkali such as concentrated ammonia added, and the liberated base separated by extraction with an organic solvent such as ether. The base may be recovered by evaporation of the solvent and purified by distillation under reduced pressure, or alternatively, if the base is a solid, by recrystallisation from a solvent wherein it is soluble (for example, petroleum ether).

Alternatively in some examples the base may be converted into its hydrochloride, by treating the dried solution of the base in a non-aqueous solvent (for example ether) with dry hydrogen chloride, when the hydrochloride separates and may be recrystallised, if necessary, from a solvent.

The manufacture of the N - disubstituted -  $\gamma\gamma$  - disubstituted -  $\gamma$  - hydroxy propylamines used as starting materials is described in the Specification of our co-pending Application for Letters Patent, No. 36258/46 (Serial No. 624,118) of even date herewith. Examples of such starting materials are  $\gamma\gamma$  - diphenyl -  $\gamma$  - hydroxy -  $\alpha$  - piperidinopropane and  $\gamma\gamma$  - diphenyl -  $\gamma$  - hydroxy -  $\alpha$  - dimethylaminopropane.

The conditions employed in the reduction may be varied. The reduction may be carried out either on the free base in solution in ethyl alcohol or other solvent or on the hydrochloride of the base dissolved in water or in ethyl alcohol or other solvent, using hydrogen at atmospheric pressure or at higher pressure, in the presence of a hydrogenation catalyst, as for example platinum black or palladised charcoal.

The manufacture by a different process of some of the N substituted -  $\gamma\gamma$  - disubstituted propylamines which may be made by the process of our invention has already been described, for example  $\gamma\gamma$  - diphenyl-

$\alpha$ -diethylaminopropane (Eisleb, *Berichte*, 1941, volume 74B, page 1433) and  $\gamma$ -diphenyl- $\alpha$ -piperidinopropane (Schaumann, *Medizin und Chemie*, 1942, volume 4, page 229). The compounds have been claimed to be highly active spasmolytic agents and to be useful in the treatment of asthma. By research and experiment we have confirmed the correctness of this claim and have also demonstrated that the allylamines prepared in accordance with this invention likewise have valuable anti-spasmodic, anaesthetic and bronchodilating activity.

The invention is illustrated by the following examples:—

#### EXAMPLE 1.

3 - N - Piperidino - 1:1 - diphenylpropan - 1 - ol hydrochloride (15 grams) is dissolved in a mixture of concentrated aqueous hydrochloric acid (30 cubic centimetres) and glacial acetic acid (100 c.c.s) and the solution boiled under reflux for 30 minutes. The solution is then evaporated to dryness under reduced pressure, the residual solid dissolved in water and the free base liberated by addition of excess ammonia solution and separated by extraction with ether. The ether solution is dried over anhydrous sodium sulphate, the ether evaporated, and the residual oil distilled under reduced pressure, 3 - N - piperidino - 1:1 - diphenylprop - 1 - ene being collected as a colourless liquid, boiling point 138°C. at 0.1 millimetres pressure.

Dry hydrogen chloride is passed through a solution of the base (10 g.) in chloroform (20 c.c.s) until acid to congo red, and anhydrous ether is added until crystallisation commences. After standing for several hours, the precipitate of 3 - N - piperidino - 1:1 - diphenylprop - 1 - ene hydrochloride is filtered off. After recrystallisation from a mixture of chloroform and acetone, the salt has melting point 209—210°C.

The hydrochloride (5 g.) is ethanol (50 c.c.s) is shaken at room temperature with platinum oxide (0.1 g., prepared according to the directions given in *Organic Syntheses*, 1932, Collective Volume 1, p. 452) in an atmosphere of hydrogen. When the theoretical amount of hydrogen has been absorbed (after approximately 3 hours), the catalyst is removed by filtration and the ethanol evaporated under reduced pressure. The crystalline residue is recrystallised from a mixture of ethanol and acetone, when 3 - N - piperidino - 1:1 - diphenylpropane hydrochloride is obtained, melting point 215—217°C. The base, liberated from the hydrochloride by treatment with

aqueous alkali, has melting point 40—41°C.

#### EXAMPLE 2.

3 - Dimethylamino - 1:1 - diphenylpropan - 1 - ol (6.0 g.) is dissolved in concentrated hydrochloric acid (18 c.c.s) and glacial acetic acid (60 c.c.s) and the solution boiled under reflux for 20 minutes. The product is then worked up as described in Example 1, when 3 - dimethylamino - 1:1 - diphenylprop - 1 - ene is obtained as a colourless oil, boiling point 192—3°C./18 mms. The hydrochloride prepared therefrom has melting point 168—170°C. (recrystallised from a mixture of ethanol and acetone).

3-Dimethylamino - 1:1 - diphenylprop - 1 - ene (5.0 g.) is dissolved in ethanol (20 c.c.s.), 3% palladised charcoal (1.5 g.) added and the mixture shaken in an atmosphere of hydrogen until no further absorption occurs. The catalyst is filtered off, the alcohol removed from the filtrate by evaporation, and the residual oil fractionally distilled under reduced pressure. 3 - Dimethylamino-1:1-diphenylpropane distils at 183—185°C./16 mms., and crystallises on standing, melting point 44—45°C. (recrystallised from light petroleum).

#### EXAMPLE 3.

3-Diethylamino - 1:1 - diphenylpropan - 1 - ol hydrochloride is dehydrated by the method described in Example 1. 3-Diethylamino - 1:1 - diphenylprop - 1 - ene is obtained as a colourless oil, becoming pale yellow on standing, boiling point 111°C./0.05 mms. The hydrochloride prepared therefrom has melting point 146—147°C. recrystallised from anhydrous acetone).

3 - Diethylamino - 1:1 - diphenylprop - 1 - ene hydrochloride (6.0 g.) in ethanol (15 c.c.s) to which 3% palladised charcoal (2.0 g.) is added is shaken in an atmosphere of hydrogen until the calculated volume is absorbed (approximately 1 hour). After removal of the catalyst by filtration, ether is added to the filtrate until crystallisation of the 3-diethylamino - 1:1 - diphenylpropane hydrochloride commences. The salt has melting point 145.5°C., and may be recrystallised from acetone.

#### EXAMPLE 4.

3 - N - Pyrrolidino - 1:1 - diphenylpropan - 1 - ol is dehydrated by the method described in Example 2. The product, 3 - N-pyrrolidino - 1:1 - diphenylprop - 1 - ene is obtained as a colourless oil, boiling point 125°C./0.02 mms., from which the hydrochloride, melting point 165—167°C. (recrystallised from a mixture of ethanol and ethyl acetate) is obtained.

The hydrochloride, when hydrogenated

by the method described in Example 3, yields 3-N-pyrrolidino - 1:1 - diphenylpropane hydrochloride of melting point 135—136°C. (recrystallised from a mixture of ethanol and ethyl acetate); the base obtained from the hydrochloride by treatment with aqueous alkali, has boiling point 125°C./0.02 mms.

#### EXAMPLE 5.

3-N-Morpholino - 1:1 - diphenylpropan - 1 - ol (6 g.) is dissolved in concentrated hydrochloric acid (18 c.c.s) and glacial acetic acid (60 c.c.s) and the solution boiled under reflux for 1 hour. The solution is then evaporated to dryness under reduced pressure, the residue dissolved in water and basified by addition of excess aqueous ammonia. The oil which separates crystallises on standing, and is removed by filtration and is washed with water. After crystallisation from ethanol, the product 3-N-morpholino - 1:1-diphenylprop-1-ene has melting point 70—72°C.; the hydrochloride prepared therefrom has melting point 218—219°C. (recrystallised from ethanol).

The hydrogenation of the hydrochloride, carried out using platinum oxide catalyst as described in Example 1 yields 3-N-morpholino - 1:1 - diphenylpropane hydrochloride, melting point 208—209°C. (recrystallised from a mixture of ethanol and ethyl acetate).

#### EXAMPLE 6.

Dehydration of 3-dimethylamino - 1:1-diphenylbutan - 1 - ol hydrochloride in a similar manner to that described in Example 1 yields 3-dimethylamino - 1:1-diphenylbut - 1 - ene, boiling point 194—196°C./19 mms., hydrochloride, melting point 160—161°C. (recrystallised from ethyl acetate). Hydrogenation is effected by shaking a solution of the hydrochloride (4.0 g.) in ethanol (20 c.c.s) with 3% palladised charcoal (2.0 g.) in an atmosphere of hydrogen. When hydrogen absorption has ceased, the catalyst is removed by filtration and the filtrate evaporated to dryness. The residue is dissolved in water, basified with aqueous ammonia and the oil separated by chloroform. After drying and evaporating the chloroform, the product, 3 - dimethylamino - 1:1 - diphenylbutane is distilled under reduced pressure, when it is obtained as a colourless oil, boiling point 176°C./12 mms. The hydrochloride obtained therefrom has melting point 157—158°C.

#### EXAMPLE 7.

3-Diethylamino - 1:1 - di - *p* - tolylpropan - 1 - ol hydrochloride is dehydrated by the method described in Example 1, when 3 - diethylamino - 1:1 - di - *p* - tolylprop - 1 - ene is obtained as a colourless

liquid, boiling point 146—150°C./0.3 mms. pressure. The hydrochloride prepared from the base has melting point 179—180°C. (recrystallised from anhydrous acetone).

Hydrogenation of the hydrochloride by the method described in Example 3 yields 3 - diethylamino - 1:1 - di - *p* - tolylpropane hydrochloride, melting point 136—138°C. (recrystallised from ethyl acetate).

#### EXAMPLE 8.

3-Diethylamino - 1 - cyclohexyl - 1 - phenylpropan - 1 - ol hydrochloride is dehydrated as described in Example 1, to give an unsaturated amine of boiling point 123—125°C./0.3 mms. pressure, from which the hydrochloride, melting point 157—160°C. (recrystallised from ethyl acetate) is obtained.

The hydrochloride when subjected to hydrogenation by the method described in Example 6, is converted into 3-diethylamino - 1 - cyclohexyl - 1 - phenylpropane (boiling point 190—192°C./18 mms. pressure). The hydrochloride prepared therefrom has melting point 125—126°C. (recrystallised from ethyl acetate).

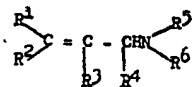
#### EXAMPLE 9.

Dehydration of 3 - diethylamino - 1-benzyl - 1 - phenylpropan - 1 - ol hydrochloride by the method described in Example 1 yields an unsaturated amine, which is obtained as a colourless oil on distillation under reduced pressure (boiling point 120—123°C./0.04 mms.). The hydrochloride obtained from the amine has melting point 157—159°C. after several recrystallisations from a mixture of ethanol and ethyl acetate.

Hydrogenation of the unsaturated amine by the method described in Example 2 yields 3 - diethylamino - 1-benzyl - 1 - phenylpropane, boiling point 112—114°C./0.02 mms. pressure, from which the hydrochloride, melting point 95—97°C. (recrystallised from ethyl acetate) is obtained.

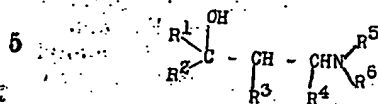
Having now particularly described and ascertained the nature of our said invention and in what manner the same is to be performed, we declare that what we claim is:—

1. A process for the production of N-disubstituted -  $\gamma\gamma$  - disubstituted allyl amines of the formula



and salts thereof comprising the removal of the elements of water (by known methods for the conversion of tertiary

alcohols into olefinic compounds by dehydration) from the corresponding N-disubstituted -  $\gamma\gamma$  - disubstituted -  $\gamma$ -hydroxy propylamines of the formula



in which the formulae  $\text{R}^1$  and  $\text{R}^2$  are aryl, aralkyl or cyclo-alkyl groups, which may be substituted by alkyl, alkoxy or other groups which are not affected by mild reduction conditions;  $\text{R}^3$  and  $\text{R}^4$  may be identical, provided that both are not aralkyl groups;  $\text{R}^5$  is hydrogen or alkyl;  $\text{R}^6$  is hydrogen, alkyl or aryl (optionally substituted as above);  $\text{R}^5$  and  $\text{R}^6$  are identical or different and are alkyl or aryl, or  $-\text{NR}^5\text{R}^6$  may denote the piperidino-, pyrrolidino- or morpholino- groups.

2. The process claimed in claim 1 wherein the substituted amino tertiary alcohol or a salt thereof is dissolved in a mixture of acetic acid and concentrated aqueous hydrochloric acid and the solution refluxed for a period of 15 minutes to one hour.

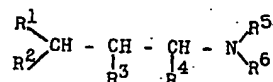
3. The process claimed in claim 1 or claim 2 wherein after dehydration of the tertiary alcohol the solution contained in the product is evaporated to dryness under reduced pressure, the residue is dissolved in water, excess of an alkali such as concentrated ammonia is added, and the liberated base is separated by extraction with an organic solvent such as ether.

4. The process claimed in claim 3 wherein the liberated base is recovered by evaporation of the solvent and distillation under reduced pressure or if the base is solid by recrystallisation from a solvent.

5. The process claimed in claim 3 wherein the base is converted into its hydrochloride by treating the dried solu-

tion of the base in a non-aqueous solvent with dry hydrogen chloride, thereby precipitating the base in the form of its hydrochloride and separating the latter 45 from the solution.

6. The process claimed in claim 1 wherein the substituted allylamines prepared in accordance therewith are converted into N-disubstituted -  $\gamma\gamma$  - disubstituted propylamines of the formula 50



(wherein  $\text{R}^1$ ,  $\text{R}^2$ ,  $\text{R}^3$ ,  $\text{R}^4$ ,  $\text{R}^5$  and  $\text{R}^6$  have the same meaning as above) by reduction under mild conditions. 55

7. The process claimed in claim 6 wherein the reduction is carried out upon the base or its hydrochloride dissolved in water, ethyl alcohol or other solvent by the action of hydrogen in the presence of a hydrogenation catalyst. 60

8. The process claimed in claim 7 wherein the reduction is carried out at atmospheric pressure and the hydrogenation catalyst is platinum black or palladised charcoal. 65

9. The process of preparing N-disubstituted -  $\gamma\gamma$  - disubstituted allylamines and N - disubstituted -  $\gamma\gamma$  - disubstituted propylamines of the general formulae hereinbefore given substantially as hereinbefore described in any of the Examples hereinbefore given. 70

10. N - disubstituted -  $\gamma\gamma$  - disubstituted allylamines and N - disubstituted -  $\gamma\gamma$  - disubstituted propylamines having the general formulae hereinbefore given when prepared by the process claimed in any preceding claim. 75

Dated this 3rd day of December, 1947.  
G. H. FRAZER,  
Chartered Patent Agent.

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